Patent
Attorney's Docket No. 033072-022

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Larry S. Barak, et al.	)	Group Art Unit: 1645
	)	
Application No.: 10/054,616	)	Examiner: Unassigned
	)	
Filed: January 22, 2002	)	
	)	Confirmation No.: 7096
For: Constitutively Desensitized G Protein-Coupled Receptors	)	

SUBMISSION OF SUBSTITUTE DRAWINGS

Box: MISSING PART
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In complete response to the Notice to File Missing Parts of Application filed under 37 C.F.R. § 1.53(b) dated April 16, 2002, enclosed please find 27 sheets of substitute drawings for review by the Patent and Trademark Office, Should the enclosed drawings require changes, it is respectfully requested that the Patent and Trademark Office notify the undersigned of same.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: M. M. Hayworth
Melissa M. Hayworth
Registration No. 45,774

P.O. Box 1404
Alexandria, Virginia 22313-1404
(919) 941-9240

Date: June 17 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 6-17-02
Date
S. Paye
(Typed or printed name of person signing the certificate)
S. Paye
(Signature of person signing the certificate)
6-17-02
(Date of Signature)

(5/01)

FIG. 1A

Human G Protein Coupled Receptor Family
(Receptors known as of January, 1999)

CLASS	LIGAND	NUMBER	TISSUE	PHYSIOLOGY	THERAPEUTICS
•Class I					
Rhodopsin like					
	•Amine				
	•Acetylcholine (muscarinic & nicotinic)	5	Brain, Nerves, Heart	Neurotransmitter	Acuity, Alzheimer's
	•Adrenoceptors				
	•Alpha Adrenoceptors	6	Brain, Kidney, Lung	Gluconeogenesis	Diabetes, Cardiovascular
	•Beta Adrenoceptors	3	Kidney, Heart	Muscle Contraction	Cardiovascular, Respiratory
	•Dopamine	5	Brain, Kidney, GI	Neurotransmitter	Cardiovascular, Parkinson's
	•Histamine	2	Vascular, Heart, Brain	Vascular Permeability	Anti-inflammatory, Ulcers
	•Serotonin (5-HT)	16	Most Tissues	Neurotransmitter	Depression, Insomnia, Analgesic
	• Peptide				
	•Angiotensin	2	Vascular, Liver, Kidney	Vasoconstriction	Cardiovascular, Endocrine
	•Bradykinin	1	Liver, Blood	Vasodilation,	Anti-inflammatory, Asthma
	•C5a anaphylatoxin	1	Blood	Immune System	Anti-inflammatory
	•Fmet-leu-phe	3	Blood	Chemoattractant	Anti-inflammatory
	•Interleukin-8	1	Blood	Chemoattractant	Anti-inflammatory
	•Chemokine	6	Blood	Chemoattractant	Anti-inflammatory
	•Orexin	2	Brain	Fat Metabolism	Obesity
	•Nociceptin	1	Brain	Bronchodilator, Pain	Airway Diseases, Anesthetic
	•CCK (Gastrin)	2	Gastrointestinal	Motility, Fat Absorption	Gastrointestinal, Obesity, Parkinson's
	•Endothelin	2	Heart, Bronchus, Brain	Muscle Contraction	Cardiovascular, Respiratory
	•Melanocortin	5	Kidney, Brain	Metabolic Regulation	Anti-inflammatory, Analgesics
	•Neuropeptide Y	5	Nerves, Intestine, Blood	Neurotransmitter	Behavior, Memory, Cardiovascular
	•Neurotensin	1	Brain,	CNS	Cardiovascular, Analgesic
	•Opioid	3	Brain,	CNS	Depression, Analgesic
	•Somatostatin	5	Brain, Gastrointestinal	Neurotransmitter	Oncology, Alzheimer's

FIG. 1B

•Tachykinin (Substance P, NKA_1)	3	Brain Nerves	Neurohormone	Depression, Analgesic
•Thrombin	3	Platelets, Blood Vessels	Coagulation	Anti-coagulant, Anti-inflammatory
•Vasopressin-like	4	Arteries, Heart, Bladder	Water Balance	Anti-diuretic, Diabetic Complications
•Galanin	1	Brain, Pancreas	Neurotransmitter	Analgesics, Alzheimer's
•Hormone protein				
•Follicle stimulating hormone	1	Ovary, Testis	Endocrine	Infertility
•Lutropin-choriogonadotropic	1	Ovary, Testis	Endocrine	Infertility
•Thyrotropin	1	Thyroid	Endocrine	Thyroidism, Metabolism
•(Rhod)opsin				
•Opsin	5	Eye	Photoreception	Ophthalmic Diseases
•Olfactory	4(~1000)	Nose	Smell	Olfactory Diseases
•Prostanoid				
•Prostaglandin	5	Arterial, Gastrointestinal	Vasodilation, Pain	Cardiovascular, Analgesic
•Lysophosphatidic Acid	2	Vessels, Heart, Lung	Inflammation	Cancer, Anti-Inflammatory
•Sphingosine-1-phosphate	2	Most Cells	Cell proliferation	Cancer
•Leukotriene	1	White Blood Cells, Bronchus	Inflammation	Asthma, Rheumatoid Arthritis
•Prostacyclin	1	Arterial, Gastrointestinal	Platelet Regulation	Cardiovascular
•Thromboxane	1	Arterial, Bronchus	Vasoconstriction	Cardiovascular, Respiratory
•Nucleotide-like				
•Adenosine	4	Vascular, Bronchus	Multiple Effects	Cardiovascular, Respiratory
•Purinoceptors	4	Vascular, Platelets	Relaxes Muscle	Cardiovascular, Respiratory
•Cannabis	2	Brain	Sensory Perception	Analgesics, Memory
•Platelet activating factor	1	Most Peripheral Tissues	Inflammation	Anti-inflammatory, Anti-asthmatic
•Gonadotropin-releasing hormone like				
•Gonadotropin-releasing hormone	1	Reproductive Organs, Pituitary	Reproduction	Prostate Cancer, Endometriosis
•Thyrotropin-releasing hormone	1	Pituitary, Brain	Thyroid Regulation	Metabolic Regulation
•Growth hormone-inhibiting factor	1	Gastrointestinal	Neuroendocrine	Oncology, Alzheimer's
•Melatonin	1	Brain, Eye, Pituitary	Neuroendocrine	Regulation of Circadian Cycle

APPLN. FILING DATE: JANUARY 22, 2002
TITLE: CONSTITUTIVELY DESENSITIZED G PROTEIN-COUPLED RECEPTORS
INVENTOR(S): LARRY S. BARAK ET AL.
APPLICATION No.: 10/054,616

FIG. 1C

•Class II				
Secretin like				
•Secretin	1	Gastrointestinal, Heart	Digestion	Obesity, Gastrointestinal
•Calcitonin	1	Bone, Brain	Calcium Resorption	Osteoporosis
•Corticotropin releasing factor/urocortin	1	Adrenal, Vascular, Brain	Neuroendocrine	Stress, Mood, Obesity
•Gastric inhibitory peptide (GIP)	1	Adrenals, Fat Cells	Sugar/Fat Metabolism	Diabetes, Obesity
•Glucagon	1	Liver, Fat Cells, Heart	Gluconeogenesis	Cardiovascular
•Glucagon-like Peptide 1 (GLP-1)	1	Pancreas, Stomach, Lung	Gluconeogenesis	Cardiovascular, Diabetes, Obesity
•Growth hormone-releasing hormone	1	Brain	Neuroendocrine	Growth Regulation
•Parathyroid hormone	1	Bone, Kidney	Calcium Regulation	Osteoporosis
•PACAP	1	Brain, Pancreas, Adrenals	Metabolism	Metabolic Regulation
•Vasoactive intestinal polypeptide (VIP)	1	Gastrointestinal	Motility	Gastrointestinal
•Class III				
•Metabotropic Glutamate	7	Brain	Sensory Perception	Hearing, Vision
•$GABA_B$	1	Brain	Neurotransmitter	Mood Disorders
•Extracellular Calcium Sensing	1	Parathyroid, Kidney, GI Tract	Calcium Regulation	Cataracts, GI Tumors

APPLN. FILING DATE: JANUARY 22, 2002
TITLE: CONSTITUTIVELY DESENSITIZED G PROTEIN-COUPLED RECEPTORS
INVENTOR(S): LARRY S. BARAK ET AL.
APPLICATION NO.: 10/054,616

FIG. 2

(a)
Wild-type DRY motif
D = may also be, preferably, E, L, P, Q, T, I, C, G, N, V, H, or A.
Y = may also be, preferably, W, F, S, I, Q, H, G, C, L, D, or A.
R = may also be, preferably, H, or C, or another amino acid, wherein GPCR is not constitutively desensitized

(b)
Modified DRY motif
2nd amino acid = any amino acid other than R or K, preferably A, D, E, N, and H.

FIG. 3A

The mutated amino acid at the second position of the DRY motif is underlined.

VASOPRESSIN V2 RECEPTOR - (Human)
accession P30518

R137H

```
  1 MLMASTTSAV PGHPSLPSLP SNSSQERPLD TRDPLLARAE LALLSIVFVA VALSNGLVLA
 61 ALARRGRRGH WAPIHVFIGH LCLADLAVAL FQVLPQLAWK ATDRFRGPDA LCRAVKYLQM
121 VGMYASSYMI LAMTLDHHRA ICRPMLAYRH GSGAHWNRPV LVAWAFSLLL SLPQLFIFAQ
181 RNVEGGSGVT DCWACFAEPW GRRTYVTWIA LMVFVAPTLG IAACQVLIFR EIHASLVPGP
241 SERPGGRRRG RRTGSPGEGA HVSAAVAKTV RMTLVIVVVY VLCWAPFFLV QLWAAWDPEA
301 PLEGAPFVLL MLLASLNSCT NPWIYASFSS SVSSELRSLL CCARGRTPPS LGPQDESCTT
361 ASSSLAKDTS S
```

(SEQ ID NO:1)

FIG. 3B

ALPHA-1B ADRENERGIC RECEPTOR (ALPHA 1B-ADRENOCEPTOR).
(Golden hamster)
ACCESSION P18841
R143E

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDEYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:2)

R143A

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDAYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:3)

R143H

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDHYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:4)

R143N

```
  1 MNPDLDTGHN TSAPAQWGEL KDANFTGPNQ TSSNSTLPQL DVTRAISVGL VLGAFILFAI
 61 VGNILVILSV ACNRHLRTPT NYFIVNLAIA DLLLSFTVLP FSATLEVLGY WVLGRIFCDI
121 WAAVDVLCCT ASILSLCAIS IDNYIGVRYS LQYPTLVTRR KAILALLSVW VLSTVISIGP
181 LLGWKEPAPN DDKECGVTEE PFYALFSSLG SFYIPLAVIL VMYCRVYIVA KRTTKNLEAG
241 VMKEMSNSKE LTLRIHSKNF HEDTLSSTKA KGHNPRSSIA VKLFKFSREK KAAKTLGIVV
301 GMFILCWLPF FIALPLGSLF STLKPPDAVF KVVFWLGYFN SCLNPIIYPC SSKEFKRAFM
361 RILGCQCRSG RRRRRRRRLG ACAYTYRPWT RGGSLERSQS RKDSLDDSGS CMSGSQRTLP
421 SASPSPGYLG RGAQPPLELC AYPEWKSGAL LSLPEPPGRR GRLDSGPLFT FKLLGEPESP
481 GTEGDASNGG CDATTDLANG QPGFKSNMPL APGHF
```

(SEQ ID NO:5)

FIG. 3C

angiotensin II receptor, type 1 (AT1A) [Rattus norvegicus].
ACCESSION NP_112247

R126H

```
      1 MALNSSAEDG IKRIQDDCPK AGRHSYIFVM IPTLYSIIFV VGIFGNSLVV
IVIYFYMKLK
     61 TVASVFLLNL ALADLCFLLT CPLWAVYTAM EYRWPFGNHL CKIASASVTF
NLYASVFLLT
    121 CLSIDHYLAI VHPMKSRLRR TMLVAKVTCI IIWLMAGLAS LPAVIHRNVY
FIENTNITVC
    181 AFHYESRNST LPIGLGLTKN ILGFLFPFLI ILTSYTLIWK ALKKAYEIQK
NKPRNDDIFR
    241 IIMAIVLFFF FSWVPHQIFT FLDVLIQLGV IHDCKISDIV DTAMPITICI
AYFNNCLNPL
    301 FYGFLGKKFK KYFLQLLKYI PPKAKSHSSL STKMSTLSYR PSDNMSSSAK
KPASCFEVE
```

(SEQ ID NO:6)

FIG. 4A

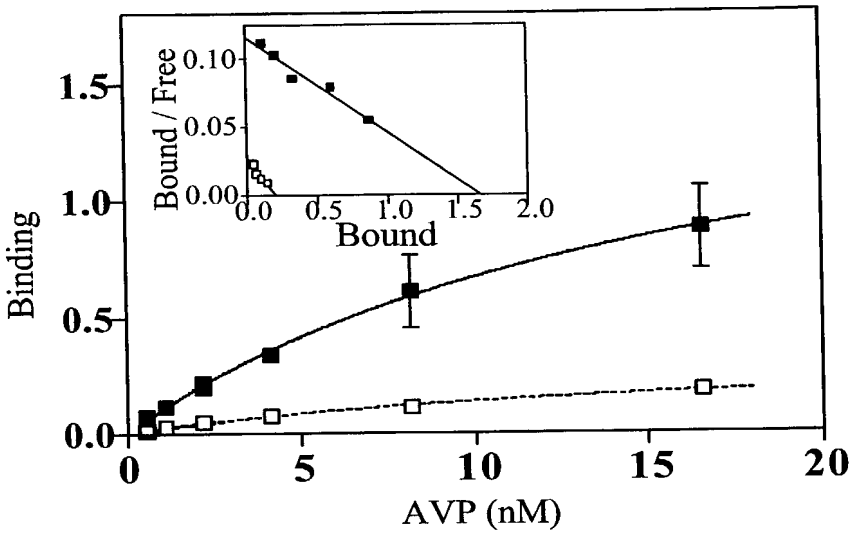
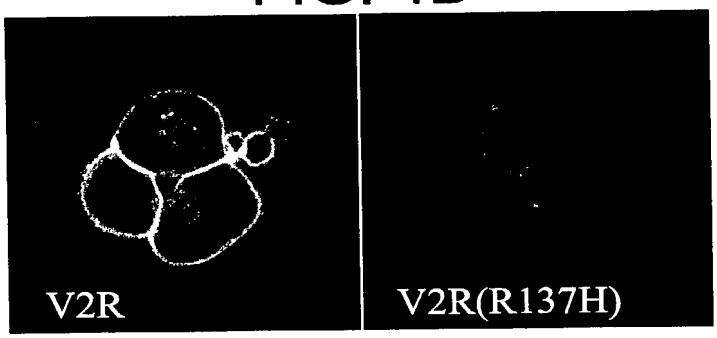
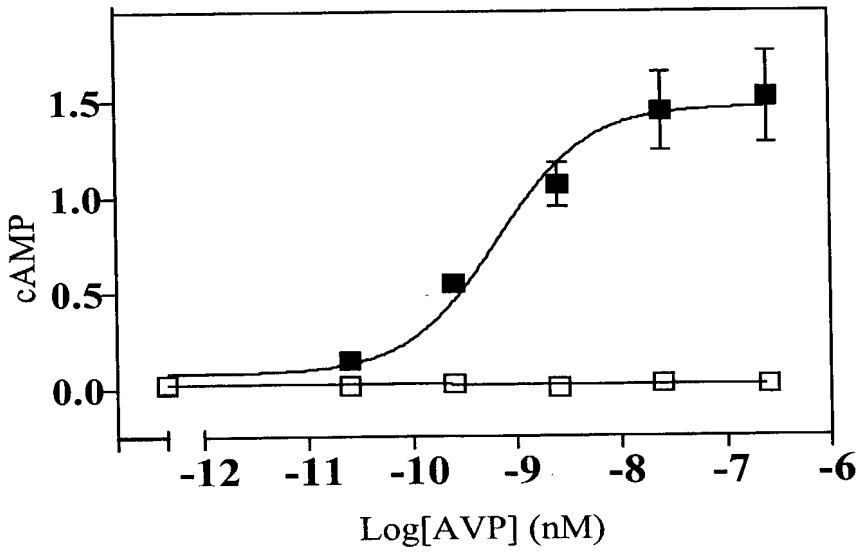


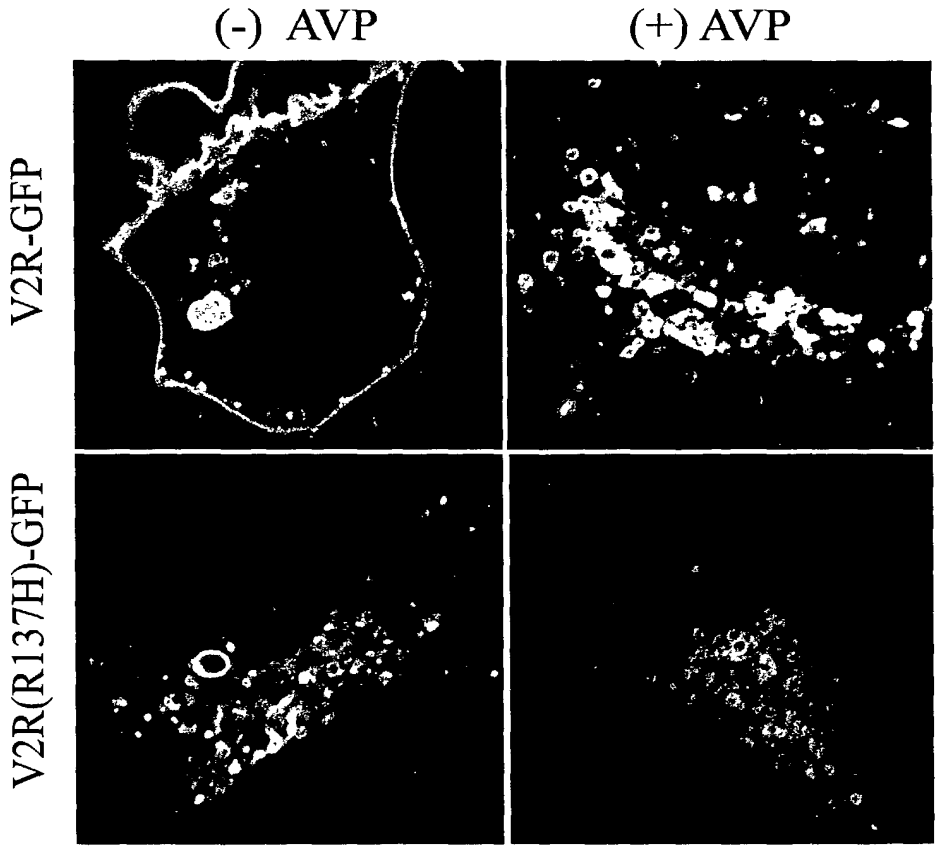
FIG. 4B



Rhodamine Anti-HA Labeling

FIG. 4C





Receptor-GFP Distribution

FIG. 5

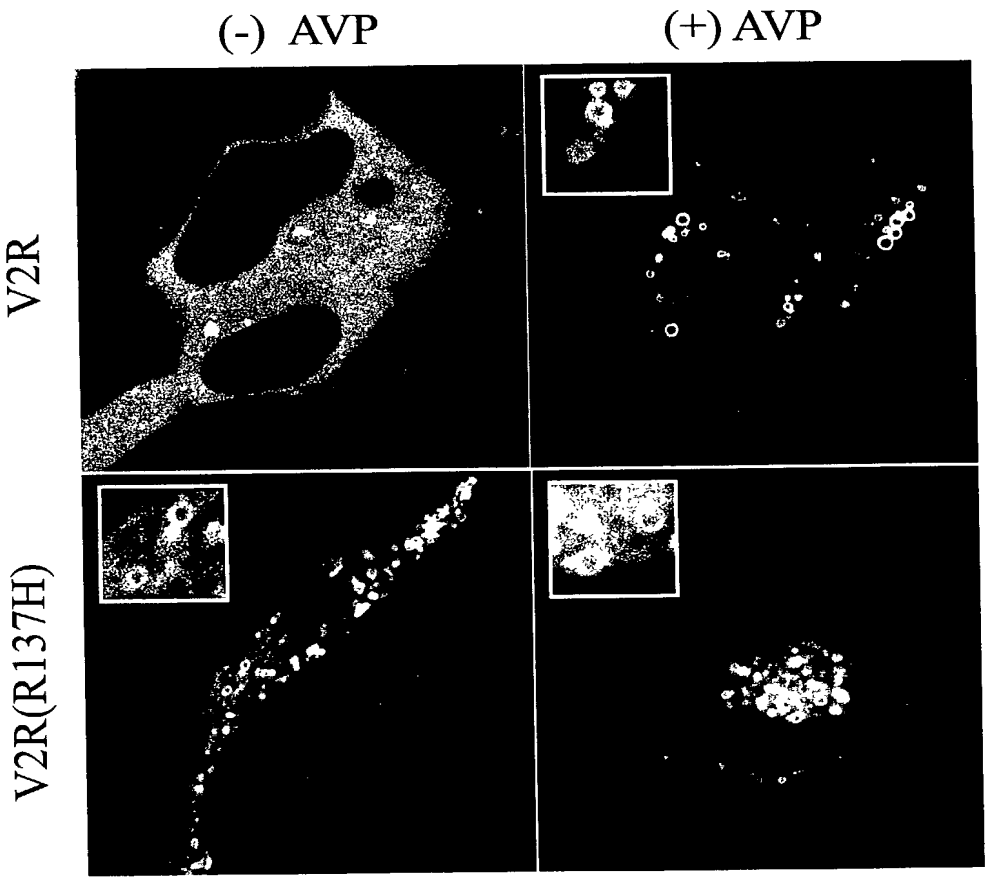


FIG. 6

βarrestin-GFP in the presence of dynamin(k44A)

FIG. 7A

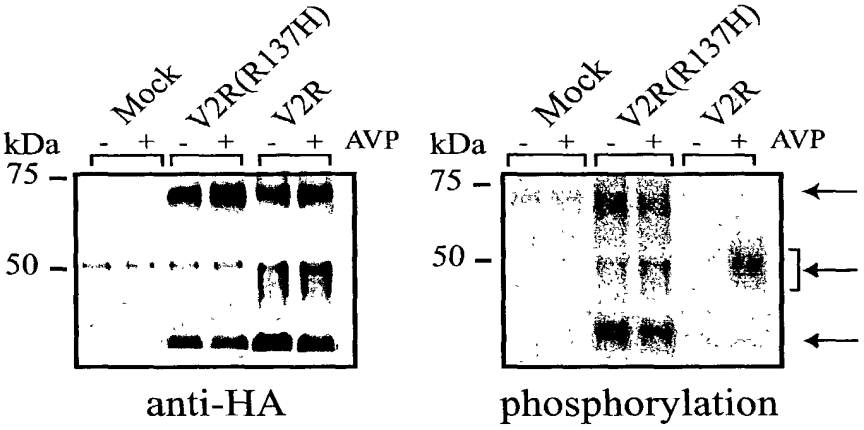
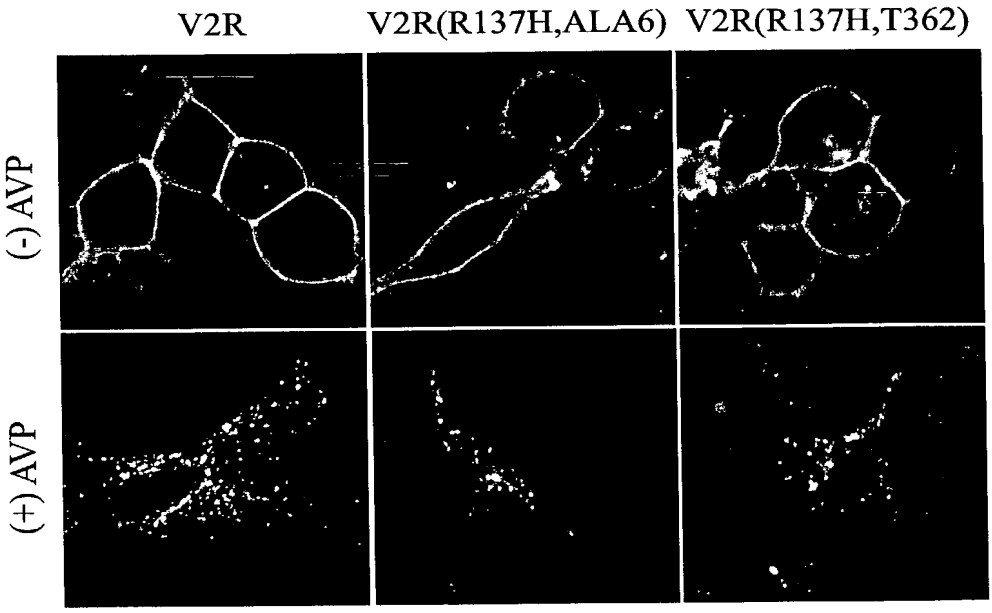


FIG. 7B

FIG. 8A



Rhodamine Anti-HA Labeling

FIG. 8B

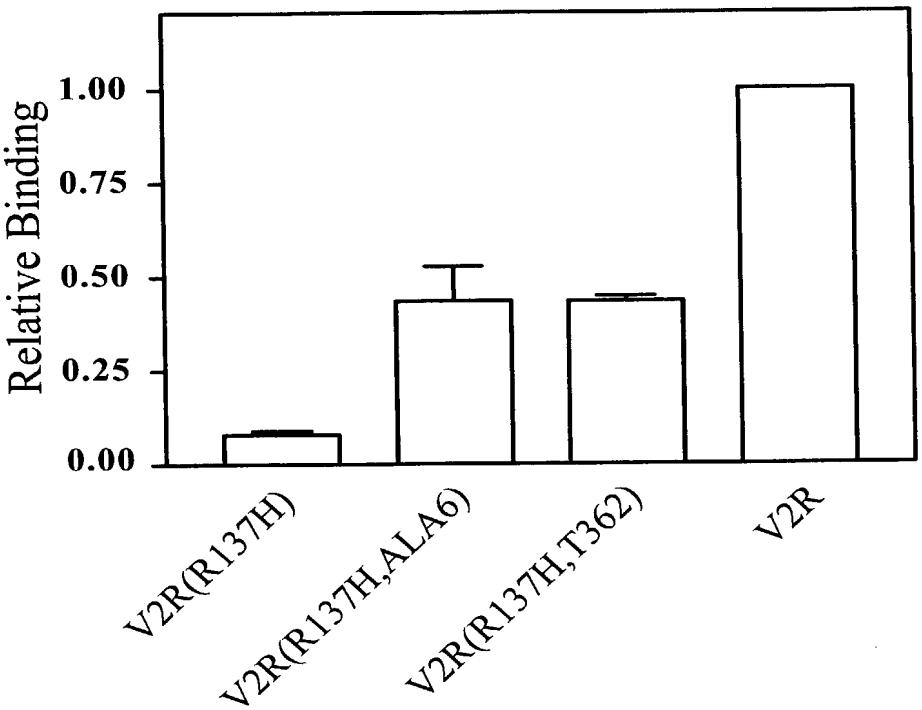


FIG 9A

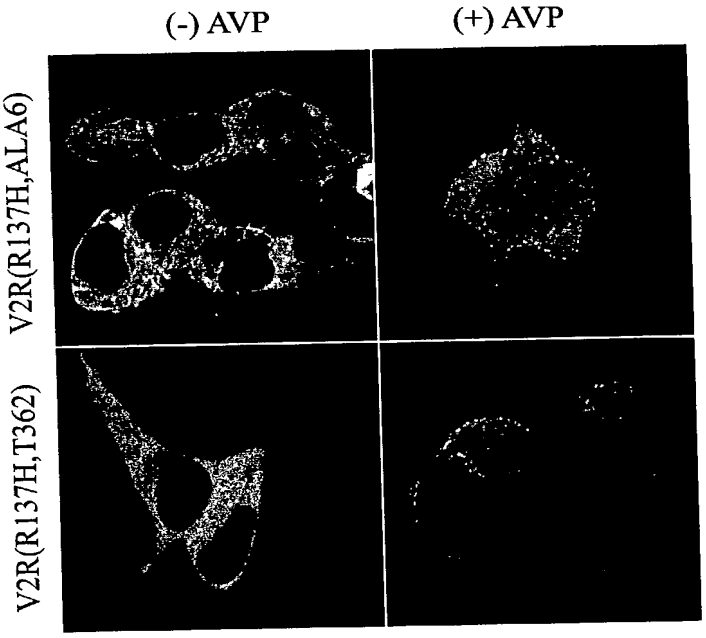
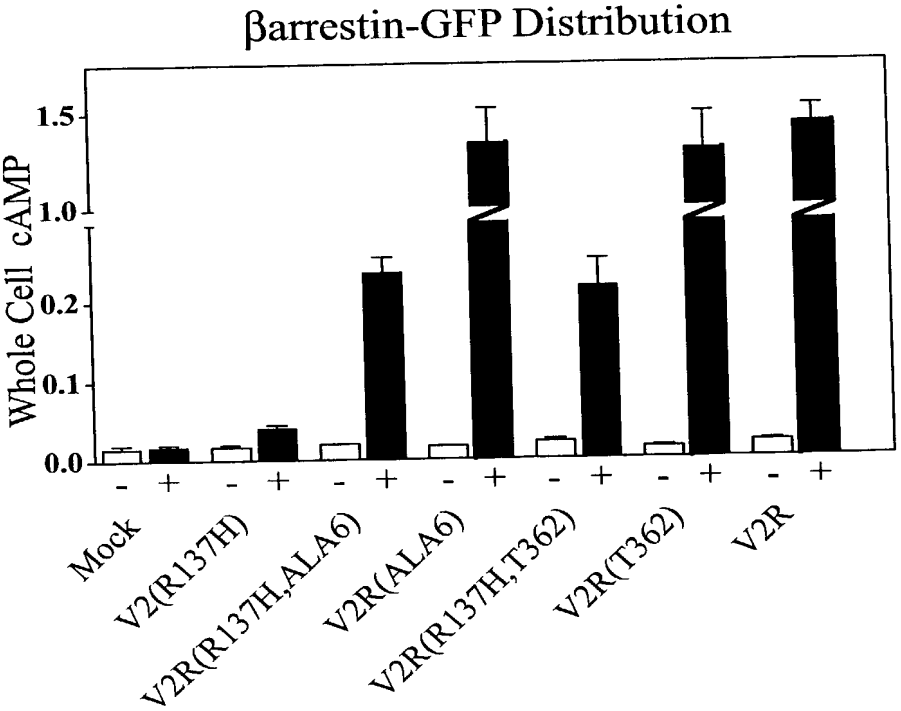

(-) AVP
(+) AVP
V2R(R137H,ALA6)
V2R(R137H,T362)

FIG 9B


βarrestin-GFP Distribution
Whole Cell cAMP
1.5
1.0
0.2
0.1
0.0
- + - + - + - + - + - + - +
Mock
V2(R137H)
V2R(R137H,ALA6)
V2R(ALA6)
V2R(R137H,T362)
V2R(T362)
V2R

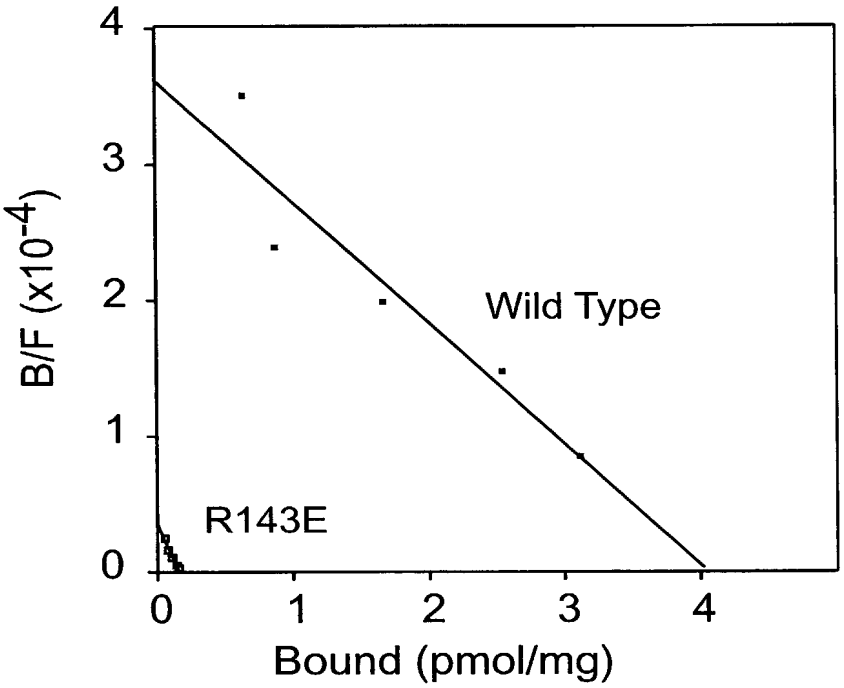
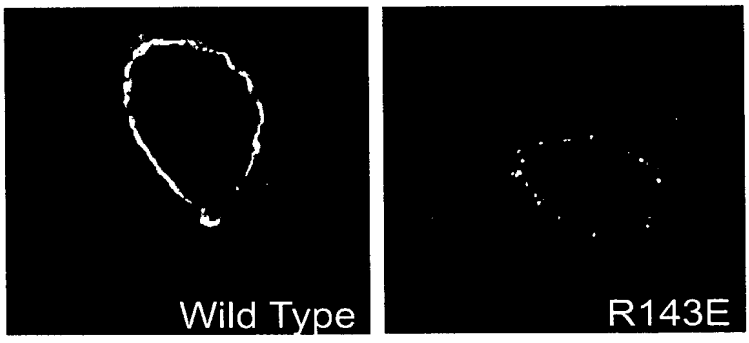


FIG. 10A



αHA-FITC

FIG. 10B

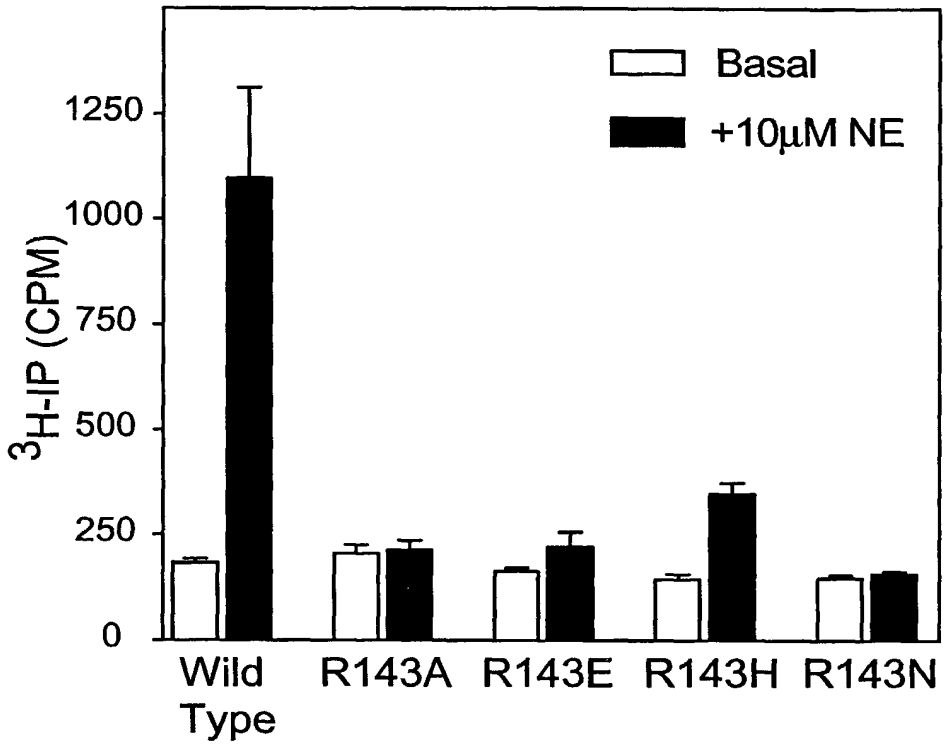

Basal
+10μM NE
^{3}H-IP (CPM)
1250
1000
750
500
250
0
Wild Type
R143A
R143E
R143H
R143N

FIG. 11

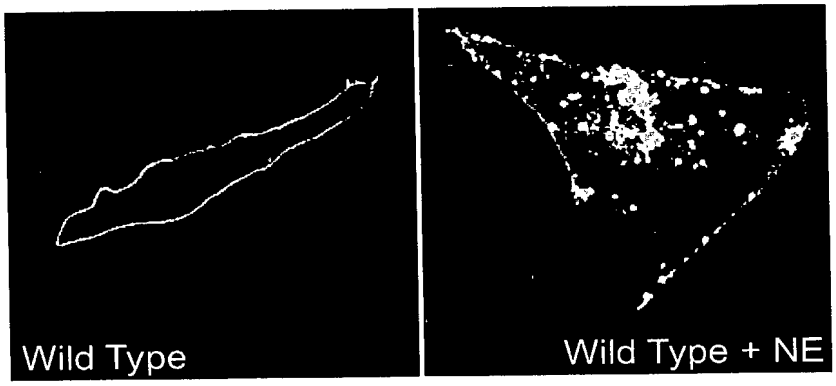
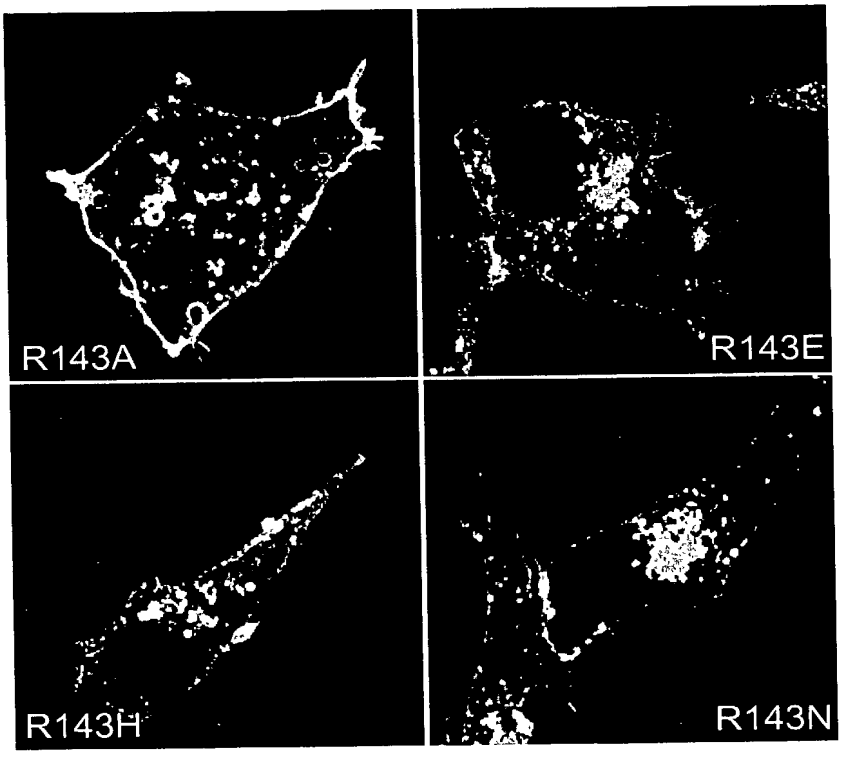


FIG. 12A



Receptor-GFP distribution

FIG. 12B

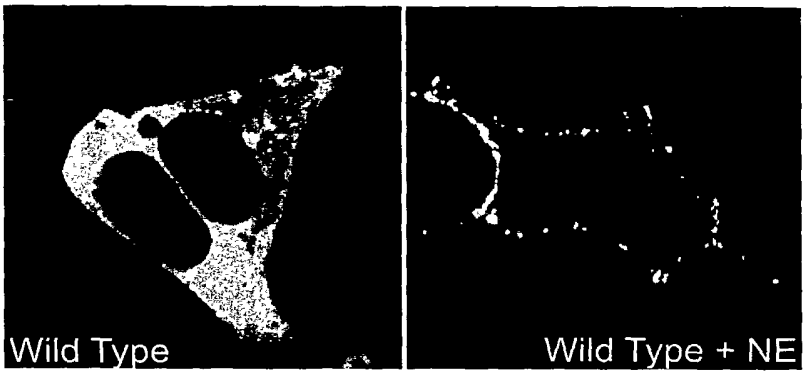
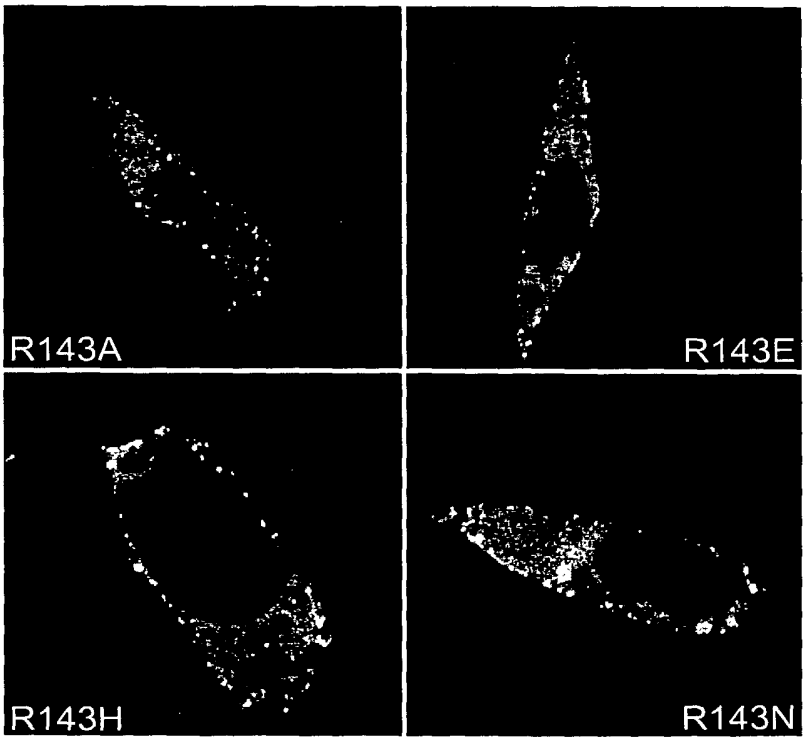


FIG. 13A



βarrestin-GFP distribution

FIG. 13B

FIG. 14A

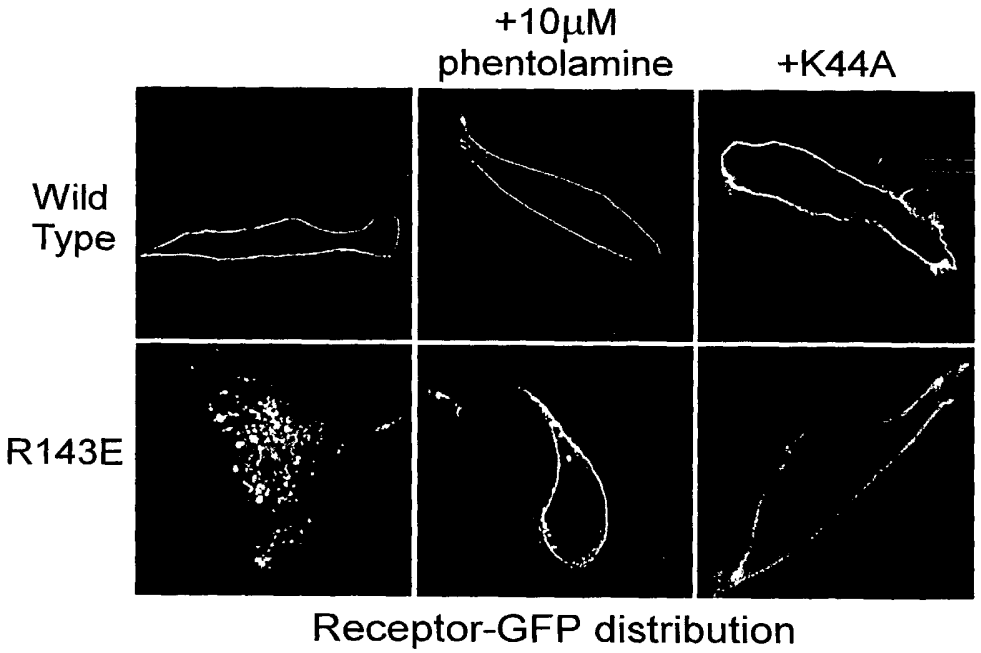
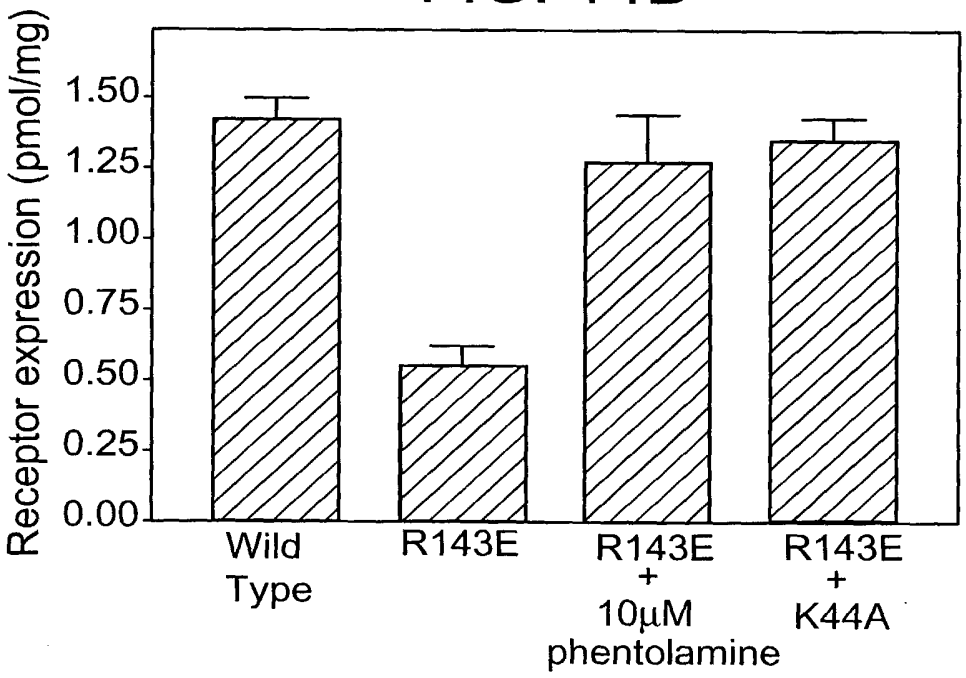
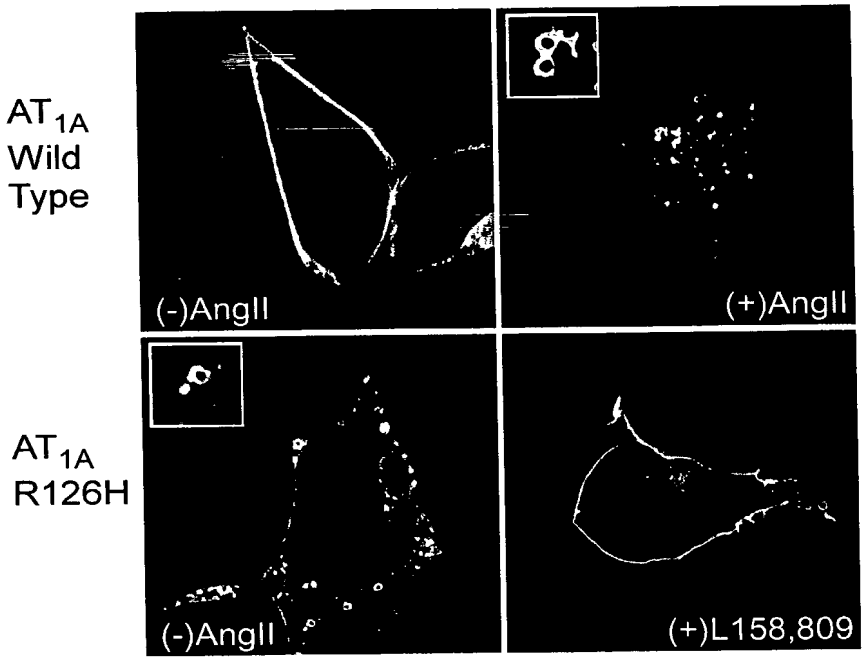


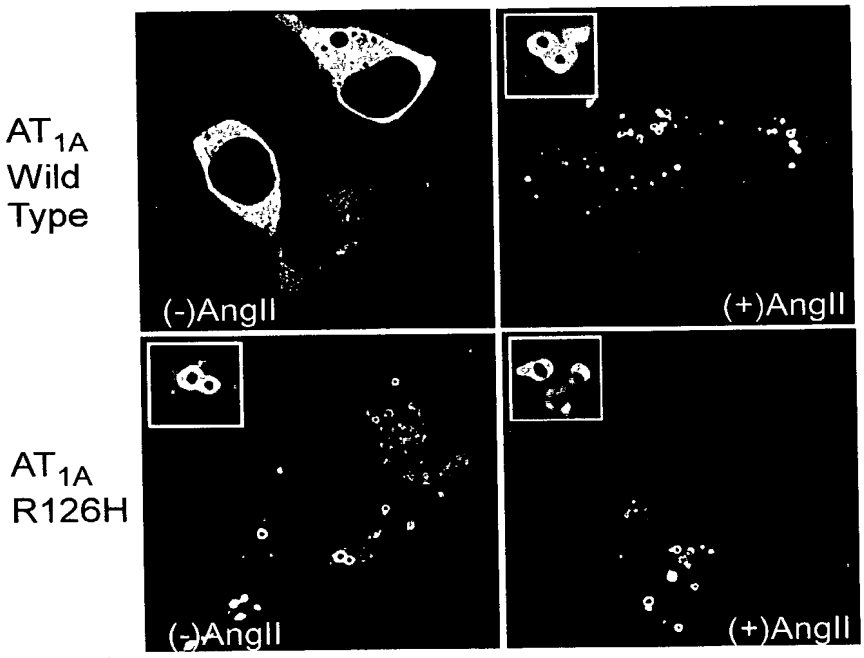
FIG. 14B





Receptor-GFP Distribution

FIG. 15A



βarrestin-GFP Distribution

FIG. 15B

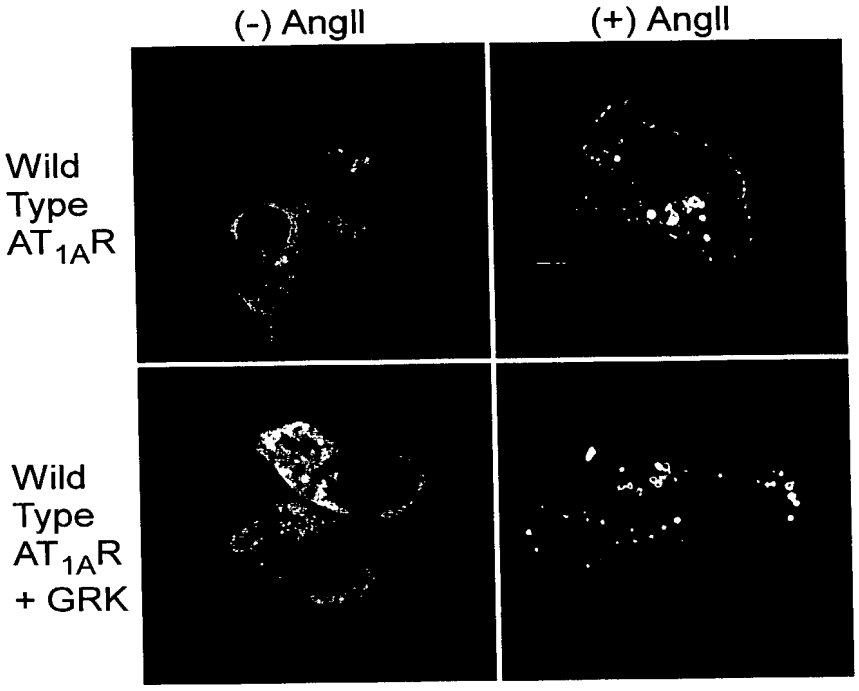


FIG. 16A

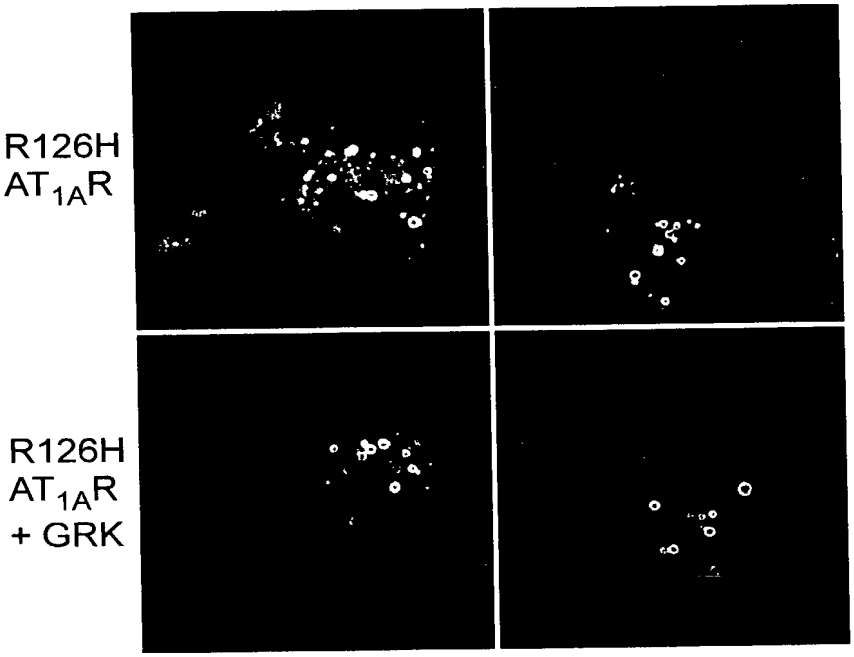


FIG. 16B

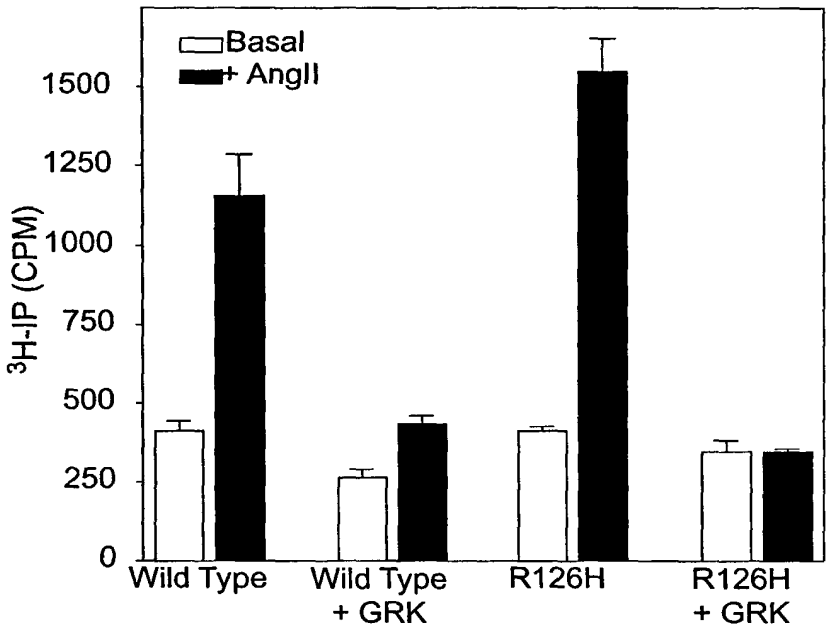

Basal
+ AngII
1500
1250
1000
750
500
250
0
^{3}H-IP (CPM)
Wild Type
Wild Type + GRK
R126H
R126H + GRK

FIG. 16C

Fig. 17A

Homo sapiens arginine vasopressin receptor 2
ACCESSION NM_000054

R137H

atgct
6 catggcgtcc accacttccg ctgtgcctgg gcatccctct ctgcccagcc
tgcccagcaa
66 cagcagccag gagaggccac tggacacccg ggacccgctg
ctagcccggg cggagctggc
126 gctgctctcc atagtctttg tggctgtggc cctgagcaat
ggcctggtgc tggcggccct
186 agctcggcgg ggccggcggg gccactgggc acccatacac
gtcttcattg gccacttgtg
246 cctggccgac ctggccgtgg ctctgttcca agtgctgccc
cagctggcct ggaaggccac
306 cgaccgcttc cgtgggccag atgccctgtg tcgggccgtg
aagtatctgc agatggtggg
366 catgtatgcc tcctcctaca tgatcctggc catgacgctg
gaccaccacc gtgccatctg
426 ccgtcccatg ctggcgtacc gccatggaag tggggctcac
tggaaccggc cggtgctagt
486 ggcttgggcc ttctcgctcc ttctcagcct gccccagctc
ttcatcttcg cccagcgcaa
546 cgtggaaggt ggcagcgggg tcactgactg ctgggcctgc
tttgcggagc cctggggccg
606 tcgcacctat gtcacctgga ttgccctgat ggtgttcgtg
gcacctaccc tgggtatcgc
666 cgcctgccag gtgctcatct tccgggagat tcatgccagt
ctggtgccag ggccatcaga
726 gaggcctggg gggcgccgca ggggacgccg gacaggcagc
cccggtgagg gagcccacgt
786 gtcagcagct gtggccaaga ctgtgaggat gacgctagtg
attgtggtcg tctatgtgct
846 gtgctgggca cccttcttcc tggtgcagct gtgggccgcg
tgggacccgg aggcacctct
906 ggaaggggcg ccctttgtgc tactcatgtt gctggccagc
ctcaacagct gcaccaaccc
966 ctggatctat gcatctttca gcagcagcgt gtcctcagag
ctgcgaagct tgctctgctg
1026 tgcccgggga cgcaccccac ccagcctggg tccccaagat
gagtcctgca ccaccgccag
1086 ctcctccctg gccaaggaca cttcatcgtg a
(SEQ ID NO:7)

FIG. 17B

Syrian golden hamster alpha-1B adrenergic receptor mRNA
ACCESSION J04084

R143H

```
        1 atgaat cccgatctgg acaccggcca caacacatca
gcacctgccc
       47 aatggggaga gttgaaagat gccaacttca ctggccccaa
ccagacctcg agcaactcca
      107 cactgcccca gctggacgtt accagggcca tctctgtggg
cctggtgctg ggcgccttca
      167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc
agtggcctgc aatcggcacc
      227 tgcggacgcc caccaactac ttcattgtca acctggccat
tgctgacctg ctgttgagtt
      287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg
ctactgggtt ctggggcgca
      347 tcttctgtga catctgggca gcggtggacg tcctgtgctg
tacggcctcc atcctgagcc
      407 tatgtgccat ctccattgat cactacattg gggtgcgcta
ctctctgcag taccccactc
      467 tggtcacccg caggaaggcc atcttggcac tcctcagtgt
gtgggttttg tccacggtca
      527 tctccatcgg gcctctcctt ggatggaaag aaccagcgcc
caacgacgac aaggaatgcg
      587 gagtcaccga agaacccttc tatgccctct tttcctccct
gggctccttc tacatcccac
      647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt
ggccaagagg accaccaaga
      707 acctggaggc tggagtcatg aaggagatgt ccaactccaa
ggagctgacc ctgaggatcc
      767 actccaagaa ctttcatgag gacaccctca gcagtaccaa
ggccaagggc cacaacccca
      827 ggagttccat agctgtcaaa ctttttaagt tctccaggga
aaagaaagca gccaaaacct
      887 tgggcattgt ggtcggaatg ttcatcttgt gttggctccc
cttcttcatc gctctcccac
      947 ttggctccct gttctccact ctcaagcccc cggacgccgt
gttcaaggtg gtattctggc
     1007 tgggctactt caacagctgc ctcaacccca tcatctaccc
gtgctccagc aaggagttca
     1067 agcgcgcctt catgcgtatc cttgggtgcc agtgccgtag
tggccgtcgc cgccgccgcc
     1127 gccgtcgtct gggcgcgtgc gcttacacct atcggccgtg
gacgcgcggc ggctcgctgg
     1187 agcgatcgca gtcgcggaag gactccctgg acgacagcgg
cagctgcatg agtggcagcc
     1247 agaggaccct gccctcggcg tcgcccagcc cgggctacct
gggtcgcgga gcgcagccac
```

1307 cactggagct gtgcgcctac cccgaatgga aatccggggc tctgctcagt ctgccagagc
1367 ctccgggtcg ccgcggtcgc ctcgactctg ggcccctctt cactttcaag ctcttgggag
1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg gggctgcgac gcaacgaccg
1487 acctggccaa tgggcagccc ggtttcaaga gcaacatgcc tctggcaccc gggcactttt
1547 ag

(SEQ ID NO:8)

FIG. 17C

R143A

1 atgaat cccgatctgg acaccggcca caacacatca gcacctgccc
47 aatggggaga gttgaaagat gccaacttca ctggccccaa ccagacctcg agcaactcca
107 cactgcccca gctggacgtt accagggcca tctctgtggg cctggtgctg ggcgccttca
167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc agtggcctgc aatcggcacc
227 tgcggacgcc caccaactac ttcattgtca acctggccat tgctgacctg ctgttgagtt
287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg ctactgggtt ctggggcgca
347 tcttctgtga catctgggca gcggtggacg tcctgtgctg tacggcctcc atcctgagcc
407 tatgtgccat ctccattgat gcctacattg gggtgcgcta ctctctgcag taccccactc
467 tggtcacccg caggaaggcc atcttggcac tcctcagtgt gtgggttttg tccacggtca
527 tctccatcgg gcctctcctt ggatggaaag aaccagcgcc caacgacgac aaggaatgcg
587 gagtcaccga agaacccttc tatgccctct tttcctccct gggctccttc tacatcccac
647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt ggccaagagg accaccaaga
707 acctggaggc tggagtcatg aaggagatgt ccaactccaa ggagctgacc ctgaggatcc
767 actccaagaa ctttcatgag gacaccctca gcagtaccaa ggccaagggc cacaacccca
827 ggagttccat agctgtcaaa ctttttaagt tctccaggga aaagaaagca gccaaaacct
887 tgggcattgt ggtcggaatg ttcatcttgt gttggctccc cttcttcatc gctctcccac
947 ttggctccct gttctccact ctcaagcccc cggacgccgt gttcaaggtg gtattctggc
1007 tgggctactt caacagctgc ctcaacccca tcatctaccc

gtgctccagc aaggagttca
1067 agcgcgcctt catgcgtatc cttgggtgcc agtgccgtag
tggccgtcgc cgccgccgcc
1127 gccgtcgtct gggcgcgtgc gcttacacct atcggccgtg
gacgcgcggc ggctcgctgg
1187 agcgatcgca gtcgcggaag gactccctgg acgacagcgg
cagctgcatg agtggcagcc
1247 agaggaccct gccctcggcg tcgcccagcc cgggctacct
gggtcgcgga gcgcagccac
1307 cactggagct gtgcgcctac cccgaatgga aatccggggc
tctgctcagt ctgccagagc
1367 ctccgggtcg ccgcggtcgc ctcgactctg ggcccctctt
cactttcaag ctcttgggag
1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg
gggctgcgac gcaacgaccg
1487 acctggccaa tgggcagccc ggtttcaaga gcaacatgcc
tctggcaccc gggcactttt
1547 ag
(SEQ ID NO:9)

FIG. 17D

R143E
1 atgaat cccgatctgg acaccggcca caacacatca
gcacctgccc
47 aatggggaga gttgaaagat gccaacttca ctggccccaa
ccagacctcg agcaactcca
107 cactgcccca gctggacgtt accagggcca tctctgtggg
cctggtgctg ggcgccttca
167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc
agtggcctgc aatcggcacc
227 tgcggacgcc caccaactac ttcattgtca acctggccat
tgctgacctg ctgttgagtt
287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg
ctactgggtt ctggggcgca
347 tcttctgtga catctgggca gcggtggacg tcctgtgctg
tacggcctcc atcctgagcc
407 tatgtgccat ctccattgat **gag**tacattg gggtgcgcta
ctctctgcag taccccactc
467 tggtcacccg caggaaggcc atcttggcac tcctcagtgt
gtgggttttg tccacggtca
527 tctccatcgg gcctctcctt ggatggaaag aaccagcgcc

caacgacgac aaggaatgcg
587 gagtcaccga agaacccttc tatgccctct tttcctccct
gggctccttc tacatcccac
647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt
ggccaagagg accaccaaga
707 acctggaggc tggagtcatg aaggagatgt ccaactccaa

ggagctgacc ctgaggatcc
767 actccaagaa ctttcatgag gacaccctca gcagtaccaa
ggccaagggc cacaacccca
827 ggagttccat agctgtcaaa ctttttaagt tctccaggga
aaagaaagca gccaaaacct
887 tgggcattgt ggtcggaatg ttcatcttgt gttggctccc
cttcttcatc gctctcccac
947 ttggctccct gttctccact ctcaagcccc cggacgccgt
gttcaaggtg gtattctggc
1007 tgggctactt caacagctgc ctcaacccca tcatctaccc
gtgctccagc aaggagttca
1067 agcgcgcctt catgcgtatc cttgggtgcc agtgccgtag
tggccgtcgc cgccgccgcc
1127 gccgtcgtct gggcgcgtgc gcttacacct atcggccgtg
gacgcgcggc ggctcgctgg
1187 agcgatcgca gtcgcggaag gactccctgg acgacagcgg
cagctgcatg agtggcagcc
1247 agaggaccct gccctcggcg tcgcccagcc cgggctacct
gggtcgcgga gcgcagccac
1307 cactggagct gtgcgcctac cccgaatgga aatccggggc
tctgctcagt ctgccagagc
1367 ctccgggtcg ccgcggtcgc ctcgactctg ggcccctctt
cactttcaag ctcttgggag
1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg
gggctgcgac gcaacgaccg
1487 acctggccaa tgggcagccc ggtttcaaga gcaacatgcc
tctggcaccc gggcactttt
1547 ag
(SEQ ID NO:10)

FIG. 17E

R143N
1 atgaat cccgatctgg acaccggcca caacacatca
gcacctgccc
47 aatggggaga gttgaaagat gccaacttca ctggccccaa
ccagacctcg agcaactcca
107 cactgcccca gctggacgtt accagggcca tctctgtggg
cctggtgctg ggcgccttca
167 tcctctttgc cattgtgggc aacatcctgg tcatcctgtc
agtggcctgc aatcggcacc
227 tgcggacgcc caccaactac ttcattgtca acctggccat
tgctgacctg ctgttgagtt
287 tcacagtcct gcccttctcc gctaccctag aagtgcttgg
ctactgggtt ctggggcgca
347 tcttctgtga catctgggca gcggtggacg tcctgtgctg
tacggcctcc atcctgagcc
407 tatgtgccat ctccattgat **aa**ctacattg gggtgcgcta
ctctctgcag taccccactc

FIG. 17E (continued)

467 tggtcacccg caggaaggcc atcttggcac tcctcagtgt gtgggttttg tccacggtca
527 tctccatcgg gcctctcctt ggatggaaag aaccagcgcc caacgacgac aaggaatgcg
587 gagtcaccga agaacccttc tatgccctct ttcctccct gggctccttc tacatcccac
647 tcgcggtcat tctggtcatg tactgccggg tctacatcgt ggccaagagg accaccaaga
707 acctggaggc tggagtcatg aaggagatgt ccaactccaa ggagctgacc ctgaggatcc
767 actccaagaa ctttcatgag gacaccctca gcagtaccaa ggccaagggc cacaacccca
827 ggagttccat agctgtcaaa ctttttaagt tctccaggga aaagaaagca gccaaaacct
887 tgggcattgt ggtcggaatg ttcatcttgt gttggctccc cttcttcatc gctctcccac
947 ttggctccct gttctccact ctcaagcccc cggacgccgt gttcaaggtg gtattctggc
1007 tgggctactt caacagctgc ctcaacccca tcatctaccc gtgctccagc aaggagttca
1067 agcgcgcctt catgcgtatc cttgggtgcc agtgccgtag tggccgtcgc cgccgccgcc
1127 gccgtcgtct gggcgcgtgc gcttacacct atcggccgtg gacgcgcggc ggctcgctgg
1187 agcgatcgca gtcgcggaag gactccctgg acgacagcgg cagctgcatg agtggcagcc
1247 agaggaccct gccctcggcg tcgcccagcc cgggctacct gggtcgcgga gcgcagccac
1307 cactggagct gtgcgcctac cccgaatgga aatccggggc tctgctcagt ctgccagagc
1367 ctccgggtcg ccgcggtcgc ctcgactctg ggcccctctt cactttcaag ctcttgggag
1427 agccggagag cccgggcacc gagggcgatg ccagcaatgg gggctgcgac gcaacgaccg
1487 acctggccaa tgggcagccc ggtttcaaga gcaacatgcc tctggcaccc gggcactttt
1547 ag

(SEQ ID NO:11)

FIG. 17F

Rattus norvegicus Angiotensin II receptor, type 1 (AT1AR)
ACCESSION NM_030985

R126H

```
1 a tggcccttaa ctcttctgct gaagatggta tcaaaagaat
      42 ccaagatgac tgccccaagg ctggcaggca cagttacata
tttgtcatga tccctaccct
      102 ctacagcatc atctttgtgg tgggaatatt tggaaacagc
ttggtggtga ttgtcattta
      162 cttttacatg aagctgaaga ctgtggccag cgtctttctt
ctcaatctcg ccttggctga
      222 cttatgcttt ttgctgactt gtcccctgtg ggcagtctat
accgctatgg agtaccgctg
      282 gcccttcggc aatcacctat gtaagatcgc ttcggccagc
gtgacgttca acctctacgc
      342 cagtgtgttc cttctcacgt gtctcagcat cgaccactac
ctggccatcg tccacccaat
      402 gaagtctcgc cttcgccgca cgatgctggt ggccaaagtc
acctgcatca tcatctggct
      462 gatggctggc ttggccagtt tgccagctgt catccaccga
aatgtatact tcatcgagaa
      522 caccaatatc acagtgtgcg cgtttcatta tgagtctcgg
aattcgacgc tccccatagg
      582 gctgggcctt accaagaata ttctgggctt cttgttccct
ttccttatca ttctcaccag
      642 ctatacccct atttggaaag ctctaaagaa ggcttatgaa
attcaaaaga acaaaccaag
      702 aaacgatgac atctttagga taattatggc gattgtgctt
ttcttcttct tttcctgggt
     762 cccccaccaa atattcactt tcctggatgt gctgattcag
ctgggcgtca tccatgactg
     822 taaaatttct gacatcgtgg acactgccat gcccatcacc
atctgcatag cgtattttaa
     882 caactgcctg aaccctctgt tctacggctt tctggggaag
aaatttaaaa agtatttcct
     942 ccagctcctg aaatatattc ccccaaaggc caagtcccac
tcaagcctgt ctacgaaaat
     1002 gagcacgctt tcttaccggc cttcggataa catgagctca
tcggccaaaa agcctgcgtc
     1062 ttgttttgag gtggagtga
```

(SEQ ID NO:12)